UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/379,308	08/23/99	DIAZ	P 016800-318

021839 HM12/0328
BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA VA 22313-1404

EXAMINER	
LUKTON, D	
ART UNIT	**PAPER NUMBER**
1653	1

DATE MAILED: 03/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/379,308	Diaz
Examiner	**Group Art Unit**
David Lukton	1653

☒ Responsive to communication(s) filed on *Feb 5, 2001*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *42-55* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *42-55* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The request filed on 9/18/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/379308 is acceptable and a CPA has been established. An action on the CPA follows.

Pursuant to the directives of paper No. 14 (filed 2/5/01), claims 28-30, 34-36, 38-41 have been cancelled, and claims 42-55 added. Claims 42-55 are pending.

Applicants' arguments filed 2/5/01 have been considered and found not persuasive.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have submitted an abstract (paper No. 11, filed 9/18/00), Michel Demarchez has presented a few results of *in vitro* studies, and offered general conclusions based thereon. First, the declaration makes reference to Bailly (*Skin Pharmacol* **3**, 256, 1990). This reference discloses experiments in which various compounds were tested for their propensity to induce secretion of plasminogen activator (PA) in F9 murine embryonal

carcinoma cells. The reference also states that the induction of PA secretion correlates with morphological changes occuring in treated embryonal carcinoma cells, and provides a means to monitor F9 differentiation. The authors of the article applied the label "retinoid" to the tested compounds. Also stated (p. 264) is that (a) it is not known which RA receptors are involved in the induction of PA in F9 cells, (b) the mechanism of PA induction by retinoids has not been elucidated, and (c) the capacity of each retinoid to induce a biological response... is not related to either the AC_{50} parameter or to receptor affinity. Notably absent is even an assertion that any of the disorders recited in claims 42-55 can be successfully treated by any of their tested compounds. Next, the declaration argues that, using assays described in Levin (*Nature* **355** 359, 1992) and in Allenby (*Proc. Natl. Acad. Sci.* **90**, 30, 1993), two of the compounds of claims 42-55 were tested for RXR binding, "RXR transactivation", and "RXR transactivation AC". It is not clear what is meant by "RXR transactivation", and "RXR transactivation AC"; perhaps applicants prepared a CRBPII-RXRE-CAT reporter plasmid, and perhaps not. It is also not clear exactly what "RXR binding" refers to; Levin makes reference to three subtypes of RAR receptors, i.e., RARα, RARβ, RARγ. Which receptor subtypes are encompassed by the term "RXR binding" ...? Is this RXRα, or a mixture of subtypes?

Next, the declaration points to Safonova (*Biochem Biophys Res Commun* **204**, 498, 1994), and argues that this reference discloses the usage of "such agonists" on cell differentiation and potential therapeutic utility. This reference discloses that a compound to which the

label "retinoid" has been applied stimulated glycerol-3-phosphate dehydrogenase activity, and that the compound "CD367" stimulated expression of RARα, RARβ, and RARγ. It is not clear that the "such agonists" disclosed in Safonova are the same as the "such agonists" disclosed in Bailly, Allenby or Levin, but even if they are, Safonova does not assert that any of the compounds which stimulate ~~stimulated~~ glycerol-3-phosphate dehydrogenase activity, or which stimulate expression of RARα, RARβ, and RARγ can be used to treat even one of the disorders recited in instant claims 42-55.

Next, the declaration has pointed to Hong (*Retinoids and Human Cancer*, 1994). No pages numbers are given. However, the copy of pages 598-623 does not show that there is even one compound which exhibits any of the *in vitro* activities described in Bailly, Allenby or Levin, nor is there an assertion that there exists a compound which exhibits any of the *in vitro* activities described in Bailly, Allenby or Levin, and at the same time can be used to treat any of the disorders recited in instant claims 42-55. It may be the case that some therapeutic utility exists for vitamin A itself, but none of the claims is drawn to a therapeutic use of vitamin A.

Next, the declaration has pointed to Lippman and DiGiovanna (Retinoids in Skin Cancer). Again, no page numbers were indicated. However, the copy of pages 179-196 (provided by applicants) was considered. The reference does discuss experiments with 13-cis retinoic acid (isotretinoin); it may well be the case that this particular agent is efficacious in the treatment of one or more dermatological disorders; but again, there is no connection

between applicants *in vitro* data, or that of Bailly, Allenby or Levin (on the one hand), and an attribution of the pharmacological effects of 13-cis retinoic acid to applicants' *in vitro* data (on the other hand).

Next, the declaration has pointed to Kavanagh (*Retinoids and Cervical Cancer*). Again, no page numbers were specified. However, pages 271-280 were considered. It is true that the authors have suggested some efficacy of all-*trans*-retinoic acid in the treatment of cervical dysplasia, and possibly some benefit following administration of 13-cis retinoic acid to patients with invasive cervical cancer. But again, it is not apparent that (a) there is a property shared by both retinoic acid and applicants' compounds that is manifest in an *in vitro* biochemical assay, and (b) that the presence or absence of this property which is so manifest correlates with the efficacy of compounds in therapeutic applications.

Next, the declaration has pointed to Meyskens (*J. Am. Acad. Dermatol.* **15**, 822, 1986). The authors do indicate that some histological changes in patients afflicted with dysplastic nevus syndrome occurred following topical administration of tretinoin. Again, no connection is drawn between applicants' *in vitro* assays, and treatment of dysplastic nevus syndrome.

What applicants have done is first, to undertake experiments which justify applying the label of "retinoid" to their compounds, and second, to point to experiments which have been done on AT retinoic acid, and 13-cis retinoic acid, and have argued that since the label "retinoid" can be applied to AT retinoic acid and 13-cis retinoic acid, that therefore any

compound to which the label "retinoid" can be applied is going to be effective in treating cancer, and all the other disorders recited in the claims. However, this argument is found to be entirely unconvincing. Certainly, the term "retinoid" is commonly used by chemists and biologists. But there is no agreed upon standard as to what the structural, biochemical or physical properties might be that are either necessary or sufficient for a compound to be classified in this way. In addition, where the line might be drawn exactly between a "retinoid" and a "non-retinoid" remains to be determined. Some chemists might apply the term "retinoid" because the UV/VIS spectrophotometric properties of a given compound are similar to retinal. Another chemist might apply the term "retinoid" because a compound shares one or more biochemical traits exhibited by 13-cis retinoic acid in halophilic bacteria (bacteriorhodopsin). Still another might apply the term "retinoid" to a compound such as all-*trans*-retinoyl fluoride because of its ability to inhibit opsin in the visual cycle (see, e.g., Wong, C. G., "Inactivation of bovine opsin by all-*trans*-retinoyl fluoride", *J. Am. Chem. Soc.* **104**, 7374-75, 1982). Another chemist might apply the term "retinoid" to a group of compounds which exhibit similar anti-oxidant activity (similar to retinol) in a given assay. A botanist may have another view entirely of what a "retinoid" is. Accordingly, merely because applicants have made an argument that the term "retinoid" can be applied to their (synthetic) compounds, and because one or two naturally occurring retinoids happen to exhibit some efficacy in the treatment of a given disease or two does not mean that applicants compounds are imbued with the property of being effective in the treatment of

even one of the disorders named in the claims. On the other hand, the possibility still remains that it is well known in the art that if a compound can induce secretion of plasminogen activator in F9 murine embryonal carcinoma cells, and can also "activate" one or more classes of RXR receptors, the compound will be effective in the treatment of one of the recited disorders, and further, that the efficacy *in vitro* correlates with the degree of efficacy *in vivo*. If a reference which teaches this is available, it might help support a claim drawn to the treatment of a specific epidermal disorder. But as matters currently stand, applicants evidence is far from being persuasive.

All of the references on pages 2-6 of the IDS have been stricken. The IDS should make it entirely clear that only the abstracts were considered. For example, the first reference on page 2 could be listed as follows:

Abstract (only) of Pol, *Int Z Vitaminforsch* **35**, 364-397, 1965.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton [phone number (703)308-3213].

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800